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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/015,534

12/13/2001

Burton G. Christensen

P-011-RC2

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06/14/2005

THERAVANCE, INC.

901 GATEWAY BOULEVARD

SOUTH SAN FRANCISCO, CA 94080

EXAMINER

SHIBUYA, MARK LANCE

ART UNIT

PAPER NUMBER

1639

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/015,534

Applicant(s)

CHRISTENSEN ET AL.

Examiner

Mark L. Shibuya

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 01 February 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 36-42 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 36-42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>5/22/05</u> | 6) <input type="checkbox"/> Other: _____ |

S.O.O.

DETAILED ACTION

1. Claims 36-42 are pending and examined.

Election/Restrictions

2. The requirement for election/restriction and applicant's election, as set forth in the prior Office action, is withdrawn. Applicant's request for reconsideration of the restriction requirement is acknowledged. Applicant's election of the Group where the linker is -alkylene-arylene-alkylene-, is taken as an election of species, because of the substantial search and administrative burden. However, the other species remain withdrawn from consideration, there being no allowable generic or linking claim.

Priority

3. Acknowledgement is made of applicant's claim that this application, filed 12/13/2001, is a continuation of U.S. Serial No. 09/493,462, filed on 1/28/2000, abandoned on 10/18/2001; which is a continuation of U.S. Serial No. 09/327,904, filed on 6/8/1999, abandoned on 1/31/2000; which application claims the benefit of U.S. Provisional Application Serial No. 60/092,938, filed 6/8/1998, and U.S. Provisional Application Serial No. 60/088,466, filed 7/16/1998.

Information Disclosure Statement

4. References B7 and B9 (IDS entered 5/22/2005), previously not considered, have now been considered.

Withdrawn Claim Objections - 35 USC § 112

5. The objection to the claims is withdrawn.

Withdrawn Claim Rejections - 35 USC § 112

6. The rejection of claims 36-40 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's amendments to the claims, entered 1/20/2005.

7. The rejection of claims 36-40 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for ligands taught by the instant specification, does not reasonably provide enablement for all ligands that bind to a cell membrane transporter or to any cell membrane transporter that are ion channels or to any sodium ion channel, is withdrawn in view of applicant's arguments, entered 1/20/2005.

8. Applicant's arguments, see Reply at p. 8, para 2, filed 1/20/2005, with respect to the rejection(s) of claim(s) 36-39 under 35 U.S.C. 102(b) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of newly found prior art references, as set forth below in new rejections under 35 U.S.C. 103(a).

9. Applicant's arguments, see Reply at p. 9, para 4, filed 1/20/2005, with respect to the rejection(s) of claim(s) 36-40 under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of newly found prior art references, as set forth below in new rejections under 35 U.S.C. 103(a).

Maintained Claim Rejections - 35 USC § 112

10. Claims 36-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a *Written Description Rejection*. This rejection maintains the reasons of record as set forth in previous Office action,

mailed 09/30/2004, and is further extended to new claims 41 and 42, and expanded upon as follows.

The specification as filed does not permit the skilled artisan to envision the claimed methods for preparing libraries of ligand compounds, having the detailed chemical structure of the encompassed genera of all divalent ligand compounds that bind to a cell membrane transporter or to cell membrane transporters that are ion channels or sodium ion channels, and where each ligand in a divalent ligand compound of the prepared library has been functionalized at different positions relative to the other functionalized ligands and linked together at those positions. The claims are not drawn to specific structures for the ligands or linkers for preparing the libraries, except in broad terms encompassing genera of organic chemistry groups.

Response to Arguments

Applicant argues that to practice the claimed invention the practitioner merely selects a ligand as a starting material from, for example, the published literature. Applicant argues that the Specification, particularly the tables and accompanying text on pages 11-27, "give hundreds, if not thousands, of specific examples of known ligands for at least 47 different cellular receptors." Applicant states that "[g]iven the extensive disclosure in Applicants' specification of many hundreds of suitable ligands for many types of cell membrane transporters, one skill in the art would clearly recognize that the inventors had possession of the claimed method at the time the application was filed."

Applicant's arguments filed 1/20/2005 have been fully considered but they are not persuasive. The claims are drawn to a method of preparing a library of compounds

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of the formula $L-X-L$, where L is a ligand and X is a linker, and in addition to selecting a ligand that binds to a cell membrane transporter, the ligands must be functionalized at different sites, so that a linker reacting with the different functional groups will provide a library of ligand compounds, where the ligands are linked at different sites. The specification discloses many examples of ligands, however, the specification does not exemplify a library of ligand compounds of the formula $L-X-L$, where the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands. The specification's disclosure of hundreds of ligands does not extend to libraries of divalent ligand compounds, where the ligands that have been functionalized at different points on the ligands and linked at those different points. As the applicant states, the disclosure provides many ligands as starting material; however, the specification does not disclose preparing a representative number of libraries by starting with the listed unmodified ligands and functionalizing them at different points, and then linking the ligands at the different points. The specification does not provide a representative number of ligand compounds where the ligands have been functionalized at different points or positions, or the linkers that connect them. Therefore, one of skill in the art would not recognize that the inventors had possession of the claimed invention.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 36-39, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Halazy et al.**, J. Med. Chem., 1996, vol. 39, pp. 4920-4927 and **Breslow et al.**, J. Am. Chem. Soc. March 28, 1998, Vol. 120, pp. 3536-3537.

Claims 36-39, 41 and 42 are drawn to a method of preparing a library of compounds of the formula: L-X-L, wherein each L is independently a ligand which binds to a cellular receptor, wherein X is a linker of the formula -alkylene-arylene-alkylene-; the method comprising the steps of: (a) identifying a ligand compound which binds to a cellular receptor; (b) providing a plurality of functionalized ligands, wherein the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands; (c) providing a linker comprising two reactive functional groups; (d) reacting the linker with the functionalized ligands to provide the library of compounds; further comprising assaying each compound of the library to determine the affinity of each compound for the cellular receptor; wherein the linker has a chain length between reactive functional groups of from about 2 Å to 100 Å; and wherein the cellular receptor is a G-protein coupled receptor. It is noted that the instant Specification at p. 31, line 28 discloses that the genus of G-protein coupled receptor includes 5-HT receptors.

Halazy et al., at the abstract, p. 4920, para 1 – p. 4921, para 4, p. 4923, Table 1 (compounds 4c, 4d, 4e) p. 4923, para 2, p. 4925, para 1, teach a method of preparing a library of compounds of the formula: L-X-L, wherein each L is independently a ligand which binds to a cellular receptor that is 5-HT (serotonin) receptor and therefore a G-protein coupled receptor, wherein X is a methyl benzyl methyl (reading on alkylene-arylene-alkylene) linker; the method comprising the steps of: (a) identifying a ligand compound which binds to a cellular 5-HT receptor; (b) providing a plurality of functionalized ligands, wherein the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands; (c) providing a linker comprising two reactive functional groups; (d) reacting the linker with the functionalized ligands to provide the library of compounds; further comprising assaying each compound of the library to determine the affinity of each compound for the cellular receptor; wherein the linker has a chain length between reactive functional groups of from about 2 Å to 100 Å.

Halazy et al., does not teach divalent ligand compounds, wherein the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands.

Breslow et al., J. Am. Chem. Soc. March 28, 1998, Vol. 120, pp. 3536-3537, throughout the publication, teach methods of making a plurality of different cyclodextrin dimer compounds, reading on a library of said compounds, and where the cyclodextrins of the compounds are linked at different relative positions.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have combined methods for producing libraries of multivalent ligand compounds that target cellular receptors comprising a linker of the formula -alkylene-arylene-alkylene-, (as taught by the reference of Halazy), where the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands, as taught by Breslow.

One of ordinary skill in the art would have been motivated to produce libraries of divalent ligand compounds comprising a linker of the formula -alkylene-arylene-alkylene-, where the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands, and wherein the libraries of divalent ligand compounds target cellular receptors, because Halazy et al., at p. 4920, para 3, teach that the so-called "bivalent ligand" approach appears very promising since many examples of molecules including two pharmacophores in a single ligand have been found to have enhanced activity and selectivity over their respective monomer counterparts; and because Breslow teaches that linking different points on the ligands permits identifying ligand compounds that bind more strongly to a target than other members of the library. One of ordinary skill in the art would have had a reasonable expectation of success in preparing the library as claimed, because ligands targeting membrane transporters, linkers and methods for functionalizing the ligands for linkage, were known in the art.

12. Claims 36-39, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Halazy et al.**, J. Med. Chem., 1996, vol. 39, pp. 4920-4927 and **Joseph-McCarthy et al.**, Proteins: Structure, Function, and Genetics 29:32-58 (1997).

Claims 36-39, 41 and 42 are drawn to a method of preparing a library of compounds of the formula: L-X-L, wherein each L is independently a ligand which binds to a cellular receptor, wherein X is a linker of the formula -alkylene-arylene-alkylene-; the method comprising the steps of: (a) identifying a ligand compound which binds to a cellular receptor; (b) providing a plurality of functionalized ligands, wherein the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands; (c) providing a linker comprising two reactive functional groups; (d) reacting the linker with the functionalized ligands to provide the library of compounds; further comprising assaying each compound of the library to determine the affinity of each compound for the cellular receptor; wherein the linker has a chain length between reactive functional groups of from about 2 Å to 100 Å; and wherein the cellular receptor is a G-protein coupled receptor. It is noted that the instant Specification at p. 31, line 28 discloses that the genus of G-protein coupled receptor includes 5-HT receptors.

Halazy et al., at the abstract, p. 4920, para 1 – p. 4921, para 4, p. 4923, Table 1 (compounds 4c, 4d, 4e) p. 4923, para 2, p. 4925, para 1, teach a method of preparing a library of compounds of the formula: L-X-L, wherein each L is independently a ligand which binds to a cellular receptor that is 5-HT (serotonin) receptor and therefore a G-protein coupled receptor, wherein X is a methyl benzyl methyl (reading on alkylene-

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arylene-alkylene) linker; the method comprising the steps of: (a) identifying a ligand compound which binds to a cellular 5-HT receptor; (b) providing a plurality of functionalized ligands, wherein the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands; (c) providing a linker comprising two reactive functional groups; (d) reacting the linker with the functionalized ligands to provide the library of compounds; further comprising assaying each compound of the library to determine the affinity of each compound for the cellular receptor; wherein the linker has a chain length between reactive functional groups of from about 2 Å to 100 Å.

Halazy et al., does not teach divalent ligand compounds, wherein the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have combined methods for producing libraries of multivalent ligand compounds that target cellular receptors comprising a linker of the formula -alkylene-arylene-alkylene-, (as taught by the reference of Halazy), where the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands, as taught by Joseph-McCarthy et al.

One of ordinary skill in the art would have been motivated to produce libraries of divalent ligand compounds comprising a linker of the formula -alkylene-arylene-alkylene-, where the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands, and wherein the libraries of divalent

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ligand compounds target cellular receptors, because Halazy et al., at p. 4920, para 3, teach that the so-called "bivalent ligand" approach appears very promising since many examples of molecules including two pharmacophores in a single ligand have been found to have enhanced activity and selectivity over their respective monomer counterparts; and because Joseph-McCarthy et al. teaches that linking different points on the ligands permits identifying ligand compounds that bind more strongly to a target than other members of the library. One of ordinary skill in the art would have had a reasonable expectation of success in preparing the library as claimed, because ligands targeting membrane transporters, linkers and methods for functionalizing the ligands for linkage, were known in the art.

13. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Halazy et al.**, J. Med. Chem., 1996, vol. 39, pp. 4920-4927 and **Breslow et al.**, J. Am. Chem. Soc. March 28, 1998, Vol. 120, pp. 3536-3537, as applied to claims 36-39, 41 and 42 above, and further in view of **Englen et al.**, (Pharmacology & Toxicology, 78: 59-68 (1996); IDS filed 5/22/2002, ref. no. C20).

Halazy et al., J. Med. Chem., 1996, vol. 39, pp. 4920-4927, at the abstract, p. 4920, para 1 – p. 4921, para 4, p. 4923, Table 1 (compounds 4c, 4d, 4e) p. 4923, para 2p. 4925, para 1, teach methods of preparing a library of bivalent compounds of the formula: L-X-L, as relied upon in the above rejection.

Breslow et al., J. Am. Chem. Soc. March 28, 1998, Vol. 120, pp. 3536-3537, teach methods wherein the functional group of functionalized ligands is located at

different positions relative to the other functionalized ligands, and is relied upon as in the rejection above.

Halazy et al. and Breslow et al. do not teach ligands that bind a muscarinic receptor.

Englen et al., (Pharmacology & Toxicology, 78: 59-68 (1996); IDS filed 5/22/2002, ref. no. C20), at the abstract and p. 59, para 1 – p. 60, para 1, Table 3, Table 4, p. 63, para 1 – p 64, para 3, Table 5, teach muscarinic antagonists that are ligands that target various types of muscarinic receptors as drugs or candidate drugs.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have combined methods for producing libraries of multivalent ligand compounds that target cellular receptors comprising a linker of the formula -alkylene-arylene-alkylene-, (as taught by the reference of Halazy), wherein the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands, (as taught by the reference of Breslow et al.), with ligands that target muscarinic receptors, (as taught by the reference of Englen).

One of ordinary skill in the art would have been motivated to have used methods wherein ligands that target muscarinic receptors were linked by linkers, because Englen et al. teach targeting muscarinic receptors for pharmaceutical purposes and because Halazy et al., at p. 4920, para 3, teach that the so-called “bivalent ligand” approach appears very promising since many examples of molecules including two pharmacophores in a single ligand have been found to have enhanced activity and selectivity over their respective monomer counterparts. One of skill in the art would

have had a reasonable expectation of success and making libraries of divalent ligand compounds that targeted muscarinic receptors, because ligands that target muscarinic receptors were known in the art.

14. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Halazy et al.**, J. Med. Chem., 1996, vol. 39, pp. 4920-4927 and **Joseph-McCarthy et al.**, Proteins: Structure, Function, and Genetics 29:32-58 (1997), as applied to claims 36-39, 41 and 42 above, and further in view of **Englen et al.**, (Pharmacology & Toxicology, 78: 59-68 (1996); IDS filed 5/22/2002, ref. no. C20).

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Joseph-McCarthy et al., Proteins: Structure, Function, and Genetics 29:32-58 (1997), teach methods wherein the functional group of functionalized ligands is located at different positions relative to the other functionalized ligands, and is relied upon as in the rejection above.

Halazy et al. and Joseph-McCarthy et al. do not teach ligands that bind a muscarinic receptor.

Englen et al., (Pharmacology & Toxicology, 78: 59-68 (1996); IDS filed 5/22/2002, ref. no. C20), at the abstract and p. 59, para 1 – p. 60, para 1, Table 3, Table

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4, p. 63, para 1 – p 64, para 3, Table 5, teach muscarinic antagonists that are ligands that target various types of muscarinic receptors as drugs or candidate drugs.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have combined methods for producing libraries of multivalent ligand compounds that target cellular receptors comprising a linker of the formula -alkylene-arylene-alkylene-, (as taught by the reference of Halazy), wherein the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands, (as taught by the reference of Joseph-McCarthy et al.), with ligands that target muscarinic receptors, (as taught by the reference of Englen).

One of ordinary skill in the art would have been motivated to have used methods wherein ligands that target muscarinic receptors were linked by linkers, because Englen et al. teach targeting muscarinic receptors for pharmaceutical purposes and because Halazy et al., at p. 4920, para 3, teach that the so-called "bivalent ligand" approach appears very promising since many examples of molecules including two pharmacophores in a single ligand have been found to have enhanced activity and selectivity over their respective monomer counterparts. One of skill in the art would have had a reasonable expectation of success and making libraries of divalent ligand compounds that targeted muscarinic receptors, because ligands that target muscarinic receptors were known in the art.

Conclusion

15. Claims 36-42 are rejected.
16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Mark L. Shibuya
Examiner
Art Unit 1639

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